

Comparison of Optimal Positive End-Expiratory Pressure and Recruitment Maneuvers During Lung-Protective Mechanical Ventilation in Patients With Acute Lung Injury/ Acute Respiratory Distress Syndrome

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BACKGROUND: In patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), the use of alveolar-recruitment maneuvers to improve oxygenation is controversial. There is lack of standardization and lack of clinical studies to compare various recruitment maneuvers. Recruitment maneuvers are closely linked to the selection of positive end-expiratory pressure (PEEP), which is also a subject of debate. **METHODS:** With 12 intubated and mechanically ventilated patients with early ALI/ARDS we conducted a recruitment maneuver (sustained inflation at 40 cm H₂O for 30 s), then set PEEP at 24 cm H₂O, and then we reduced PEEP stepwise, by 4 cm H₂O every 10 min. We kept the fraction of inspired oxygen (F_{IO₂}) at 0.8. After each PEEP decrement step we measured P_{aO₂}. We defined the “optimal” PEEP as the PEEP step above which P_{aO₂} decreased by ≥ 20%. All the patients then underwent a period of ventilation on the same settings: tidal volume 6 mL/kg, PEEP at the level set by the physician before the experiment, plateau pressure < 30 cm H₂O. Then each patient underwent 3 ventilation strategies, each applied for one hour: optimal PEEP alone; optimal PEEP plus one sustained inflation (40 cm H₂O for 30 s); and optimal PEEP plus sigh breaths (ie, twice the baseline tidal volume, plateau pressure < 40 cm H₂O) every 25 breaths. After the application of each PEEP strategy we measured arterial blood gas values and the static compliance of the respiratory system. **RESULTS:** The mean ± SD optimal PEEP was 12 ± 4 cm H₂O. The measurements from the standardization periods were comparable between the 3 PEEP groups. In the optimal-PEEP-plus-sighs group the changes in P_{aO₂} (85 ± 96%) and static compliance (14 ± 20%) were significantly greater than in the 2 other groups. **CONCLUSIONS:** Sighs superimposed on lung-protective mechanical ventilation with optimal PEEP improved oxygenation and static compliance in patients with early ALI/ARDS. *Key words:* acute respiratory distress syndrome, ARDS, acute lung injury, ALI, alveolar recruitment, low tidal volume, lung-protective mechanical ventilation, positive end-expiratory pressure, recruitment maneuvers. [Respir Care 2009; 54(7):847–854. © 2009 Daedalus Enterprises]

Introduction

In patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), lung-protective mechanical ventilation is strongly recommended, since a large

to 12 mL/kg V_T,¹ and 2 other trials of low V_T had similar results.^{2,3} Three other trials⁴⁻⁶ found no clinical benefit from limiting pressure and/or volume in patients with ARDS, but a recent systematic review recommended lung-protective ventilation for ALI/ARDS.⁷

Important questions remain. First, low-V_T mechanical ventilation does not definitively protect the lung from overdistention during tidal breath. End-inspiratory overdistention occurs in 30% of patients with ARDS receiving lung-protective mechanical ventilation, as a result of the extensive consolidated dorsal lung regions that are not recruited during the tidal breath.⁸ Second, low V_T

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randomized controlled trial showed that tidal volume (V_T) of 6 mL/kg predicted body weight and plateau pressure (P_{plat}) < 30 cm H₂O improved patient survival, compared

might cause alveolar derecruitment due to insufficient end-expiratory lung volume. Maneuvers and/or strategies that recruit alveoli might counteract those adverse effects of low V_T and improve oxygenation, but what should be the target: to maximize recruitment, or to minimize distention? And what is the best lung-recruitment method, given the various recruitment methods' different effects on the lungs?⁹ Third, there is no evidence that recruitment maneuvers impact patient outcomes. For the ALI/ARDS lung to be recruited during conventional mechanical ventilation, the airway pressure must be greater than the critical opening pressure at the end of inspiration and must be kept above the closing pressure at the end of expiration.^{10,11} Given the large range of these critical pressures across the injured lung,¹⁰⁻¹² full lung recruitment can only be obtained by increasing airway pressure to well above 30 cm H₂O, at least transiently.¹³

Positive end-expiratory pressure (PEEP) and recruitment maneuvers such as sustained inflation or sighs are common lung-recruitment strategies in ALI/ARDS. Some clinicians have used pressure-controlled ventilation and PEEP increases at a constant driving pressure.¹² These methods have not been adequately compared in patients with ALI/ARDS. Furthermore, the efficacy of a recruitment maneuver is closely linked to the selected PEEP, because PEEP is a recruitment maneuver per se, as it increases the end-inspiratory transalveolar pressure and prevents derecruitment.¹⁴ However, the definition of the optimal PEEP is still open to discussion, as 3 large randomized controlled trials found no clinical benefit from a low or a high PEEP.¹⁵⁻¹⁷ Moreover, oxygenation response depends on the sequence of application of PEEP and the recruitment maneuver; there is no significant effect on oxygenation if the PEEP is selected before the recruitment maneuver,¹⁸ whereas oxygenation improves if the recruitment maneuver is conducted before selecting the PEEP.¹⁹ Our main objective was to understand the effect of recruitment maneuvers on oxygenation in patients with ALI/ARDS. We studied whether a decremental PEEP trial could identify

an optimal PEEP and whether a sustained inflation or repeated sighs were necessary to maintain lung recruitment.

Methods

The protocol was approved by our local ethics committee (Comité Consultatif des Personnes se Prêtant à la Recherche Biomédicale Lyon B, Lyon, France).

Patients

Patients were enrolled if they were invasively mechanically ventilated for ARDS or ALI (as defined by the American/European consensus conference²⁰), and ≥ 18 years old, and had stable hemodynamics (mean systemic blood pressure ≥ 75 mm Hg with or without vasopressor), arterial catheter in place, and the next of kin provided written informed consent. The exclusion criteria were emphysema, pneumothorax, recent (< 15 d) lung surgery, or air leaks with persistent bronchopleural fistula.

Patients were orotracheally intubated with a cuffed endotracheal tube (inner diameter 7.0–8.5 mm) (Mallinckrodt, Athlone, Ireland) and mechanically ventilated (Horus, Taema, Antony, France). During the study, patients were sedated with midazolam (0.05–0.2 mg/kg/h) and sufentanyl (0.1–0.5 μ g/kg/h), and paralyzed with cisatracurium (0.2 mg/kg/h).

Protocol

Before the measurements were taken, the trachea was gently suctioned if needed, without disconnecting the ventilator circuit. The cuff was inflated to 40 cm H₂O, and checked every hour. Throughout the procedure, thorough care was provided by a physician not involved in the study. First we standardized the mechanical ventilation settings in all patients: volumetric mode, constant-flow inflation, V_T 6 mL/kg of predicted body weight, $P_{plat} < 30$ cm H₂O, ratio of inspiratory time to total respiratory cycle time 0.33, respiratory rate adjusted to keep pH > 7.30 , and fraction of inspired oxygen (F_{IO_2}) 0.8, or higher if necessary to obtain transcutaneously measured oxygen saturation $\geq 88\%$ or $P_{aO_2} \geq 55$ mm Hg. PEEP was maintained at the level set by the physician before the experiment.

The protocol had 2 parts. In the first part,²¹ PEEP was titrated in each patient as follows. We applied an airway pressure of 40 cm H₂O for 30 s, then PEEP was set at 24 cm H₂O for 10 min and V_T was adjusted to keep P_{plat} below 32 cm H₂O. PEEP was then lowered stepwise, by 4 cm H₂O each 10 min, down to zero PEEP. After each PEEP decrement we measured the arterial blood gases and static compliance of the respiratory system (C_{stat}). We defined the "optimal" PEEP as the PEEP below which P_{aO_2}/F_{IO_2} fell by at

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The authors have disclosed no conflicts of interest.

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Table 1. Entry Data and Ventilator Settings

Patient No.	Age (y)	Sex	Days on Ventilator	Cause of ALI/ARDS	P _{aO₂} /F _{IO₂}	Lung-Injury Score	V _T (mL)	V _T (mL/kg)	PEEP (cm H ₂ O)	F _{IO₂} (%)
1	55	M	1	Multiple-organ dysfunction, malaria	133	2.75	430	6	12	60
2	65	M	2	Pneumonia	113	2.75	370	6	14	70
3	51	M	2	Multiple-organ dysfunction, pneumonia	175	2.25	400	6	6	40
4	70	F	1	Alveolar hemorrhage	160	2.25	309	6	0	40
5	66	M	1	Pneumonia	150	2.25	360	6	4	80
6	58	M	1	Pneumonia	150	3.25	340	6	18	50
7	80	M	1	Pneumonia	115	2.50	309	6	8	60
8	73	F	2	Septic shock, peritonitis	250	2.00	260	6	8	45
9	75	M	1	Septic shock, aspiration	146	2.25	380	6	5	80
10	41	M	4	Septic shock, pneumonia	197	2.50	460	6	10	50
11	76	F	4	Aspiration, staphylococcal sepsis	125	3.00	299	6	10	80
12	78	F	1	Influenza	150	3.25	279	6	14	80
Mean ± SD	66 ± 12		2 ± 1		155 ± 38	2.6 ± 0.4	350 ± 61	6 ± 0	9 ± 5	61 ± 16

ALI = acute lung injury
 ARDS = acute respiratory distress syndrome
 V_T = tidal volume
 PEEP = positive end-expiratory pressure
 F_{IO₂} = fraction of inspired oxygen

least 20%. If that 20% P_{aO₂}/F_{IO₂} decrement was not obtained, we selected the PEEP that resulted in the highest P_{aO₂}.

The second part of the protocol consisted of 3 periods of one hour each, during which each patient underwent the following 3 PEEP strategies, in a random order: optimal PEEP alone; optimal PEEP preceded by a 30-s sustained inflation at 40 cm H₂O; and optimal PEEP with sighs delivered every 25 breaths. A sigh consisted of one V_T with a P_{plat} of 40 cm H₂O and a maximum of twice the standardized V_T. The sustained inflations and the sighs were delivered without disconnecting the patient from the ventilator. Before each of the 3 experimental PEEP periods, the standardized mechanical ventilation settings were resumed for 10 min. Arterial blood gas values and C_{stat} were measured at the end of each period of standard-settings ventilation and after each 60-min experimental period.

Arterial blood gases was measured with a blood-gas analyzer (248, Ciba-Corning). C_{stat} was calculated by dividing the V_T by the difference between P_{plat} and total PEEP. P_{plat} was measured 5 s after an end-inspiratory occlusion, and total PEEP was measured 3 s after an end-expiratory occlusion. The V_T values and pressures were taken from the ventilator display. C_{stat} during the optimal-PEEP-with-sighs period was measured during a regular inflation, not a sigh inflation.

Statistical Analysis

Values are expressed as mean ± SD. We used a linear mixed-effects model to compare the absolute values and the relative differences of P_{aO₂} and C_{stat} at baseline and

60 min. The 3 PEEP strategies were used to define a 3-level group variable, which was taken as the unordered experimental factor with fixed effects. The factor with random effects was composed of the 12 patients. We used analysis of variance to analyze the overall effect of the PEEP strategy group. We used Helmert contrasts to compare the effect of optimal PEEP with sustained inflation, and of optimal PEEP with sighs was compared to optimal PEEP. We conducted the statistical analyses with statistics software (R, version 2.6.2, R Project for Statistical Computing, <http://www.r-project.org>). Differences were considered significant when *P* < .05.

Results

We enrolled 12 patients with early ALI/ARDS (Table 1). We started the decremental PEEP trial at PEEP of 24 cm H₂O in 6 patients. In the other 6 patients we started at PEEP of 20 cm H₂O, because PEEP of 24 cm H₂O caused P_{plat} > 32 cm H₂O, even after lowering V_T to 4–5 mL/kg. The protocol step from 24 cm H₂O to 20 cm H₂O was therefore not done in the latter 6 patients. In patient 6, who was the most severely hypoxemic, PEEP of 8 cm H₂O caused severe oxygen desaturation, so we brought PEEP back up to 12 cm H₂O and kept it there. F_{IO₂} was eventually kept constant at 0.8 in each patient for the whole experiment (ie, the reported P_{aO₂} values were all obtained with the same F_{IO₂}).

The optimal PEEP averaged 12 ± 4 cm H₂O. It was 20 cm H₂O in 1 patient, 16 cm H₂O in 4 patients, 12 cm H₂O in 2 patients, and 8 cm H₂O in 5 patients (Fig. 1). In 2 patients

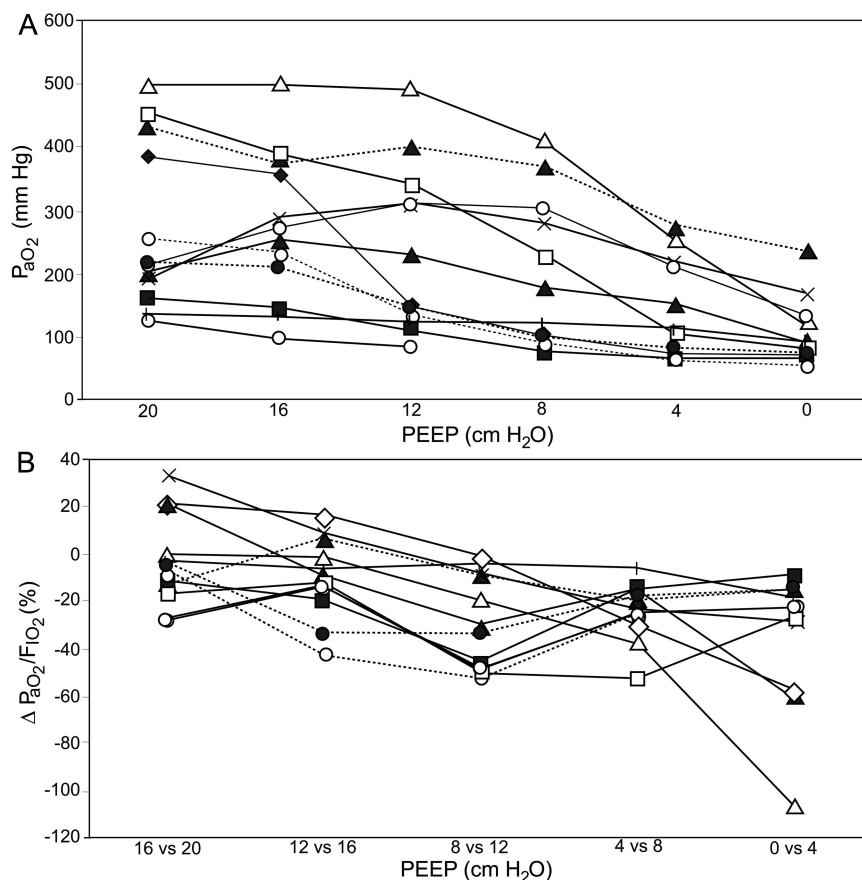


Fig. 1. A: Individual P_{aO_2} values during stepwise decrease of positive end-expiratory pressure (PEEP), starting at 20 cm H₂O cm H₂O, at a 0.80 fraction of inspired oxygen (F_{IO_2}), in 12 patients. B: Individual values of the change in the ratio of P_{aO_2} to F_{IO_2} at each PEEP level.

(8 and 9, in Fig. 2), C_{stat} progressively increased, unlike the other patients, in whom C_{stat} first increased and then decreased. On average, C_{stat} initially increased along with the early decrease in PEEP, then declined as PEEP decreased (Fig. 3). We observed no important adverse effects during or after the protocol, but 2 patients had a brief drop in blood pressure that required increasing the vasopressor dose.

For the second part of the study, the ventilation settings were kept constant: V_T 0.35 ± 0.06 L, respiratory rate 25 ± 5 breaths/min, inspiratory time 0.83 ± 0.18 s, inspiratory flow 0.43 ± 0.05 L/s. With these settings, PEEP, total PEEP, P_{plat} , oxygenation, and C_{stat} did not significantly differ between the groups during the standardized (baseline) ventilation period (Table 2). In the optimal-PEEP-with-sighs group, the mean sigh V_T was 666 ± 164 mL, which corresponded to 1.9 ± 0.21 times the baseline V_T , and the resulting P_{plat} was 34 ± 6 cm H₂O. At the end of each experimental period, P_{aO_2} and C_{stat} were significantly different in each of the 3 groups (see Table 2). The baseline and changes to the P_{aO_2} and C_{stat} (see Table 2) (Fig. 4) were significantly higher in the optimal-PEEP-with-sighs group than in the optimal-PEEP group, whereas optimal PEEP with sustained inflation had no

significant effect (see Table 2 and Fig. 4). The other variables did not differ between the groups (see Table 2).

Discussion

The main finding of the present study is that sighs superimposed on lung-protective mechanical ventilation significantly improve oxygenation and C_{stat} in patients with ALI/ARDS.

Our results confirm that lung-protective ventilation with a V_T of 6 mL/kg of predicted body weight is associated with a potential for alveolar recruitment. Some authors advocate fully recruiting and opening the lung with a maximum-recruitment strategy,¹² which involves high airway pressure to achieve and sustain the opening pressure that maintains recruitment,^{10,11} but that strategy can cause overdistention. However, Borges et al demonstrated that with this strategy overdistention did not occur and that maximum alveolar recruitment reduced the lung heterogeneity.¹² This potential alveolar recruitment can be achieved at a minimal pressure cost, as in our study, with repetitive sighs and optimal PEEP.

We defined the optimal PEEP as the PEEP that prevented derecruitment, inferred from the oxygenation pro-

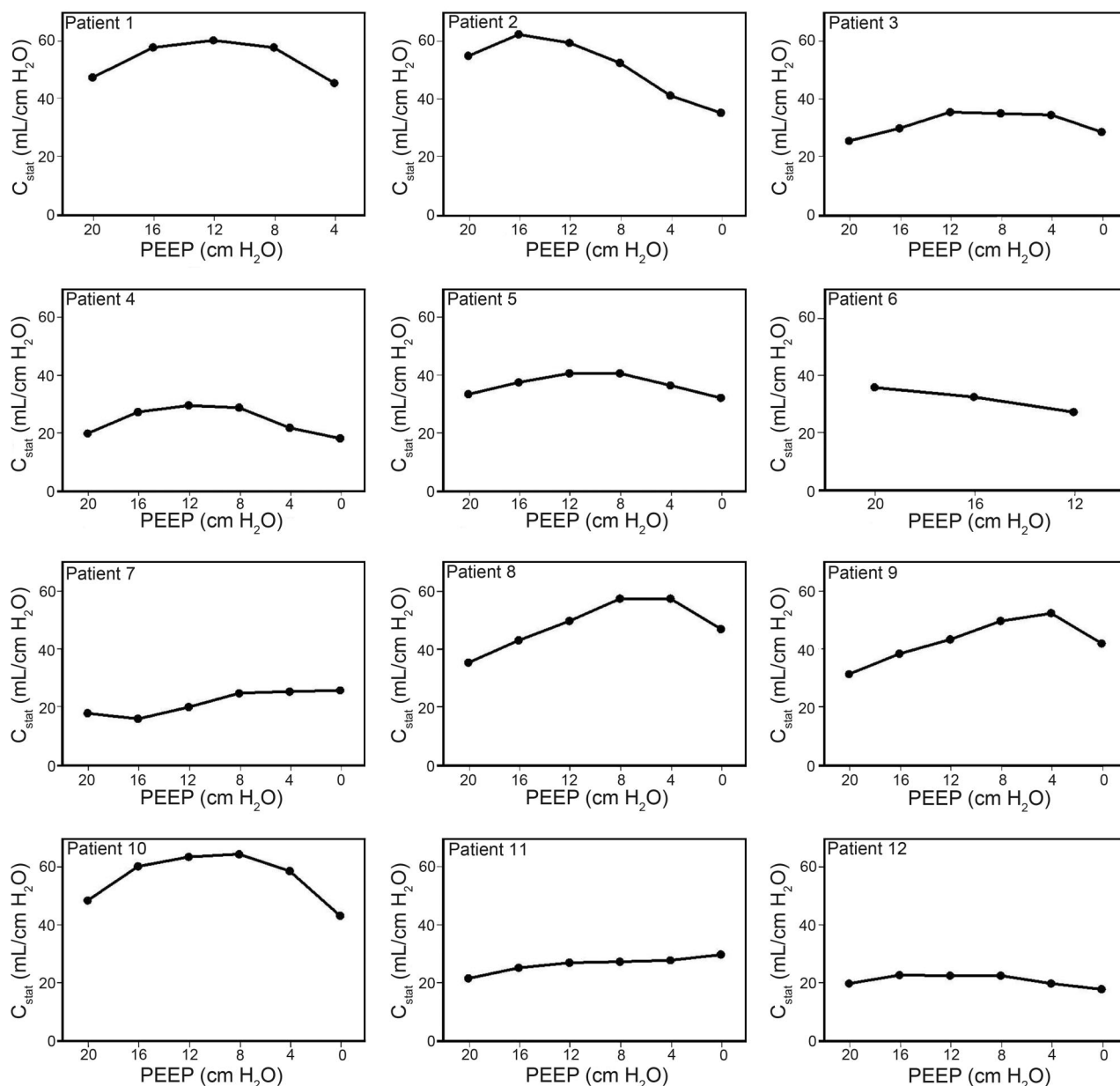


Fig. 2. Individual values of the static compliance of the respiratory system (C_{stat}) during stepwise decrease of positive end-expiratory pressure (PEEP), starting at 20 cm H₂O, in 12 patients.

file after each PEEP decrement. A recent experimental investigation that included decremental PEEP trials that started at 24 cm H₂O found that derecruitment (identified via computed tomography as a > 5% increase in lung tissue) correlated with a sudden drop in oxygenation.²¹ Furthermore, in patients with early ARDS, Borges et al found a strong hyperbolic correlation between derecruitment (assessed via computed tomography) and reduced oxygenation.¹² There are numerous ways to select PEEP at the bedside, but the decremental PEEP test is attractive because it allows PEEP titration according to the individ-

ual patient's pathophysiology. Suter et al²² defined optimal PEEP as the PEEP that maximized oxygen transport, which was associated with maximum compliance of the respiratory system. Theoretical analysis predicted that maximum compliance during a decremental PEEP trial would coincide with the open-lung PEEP.²³ In the present study C_{stat} first increased as the PEEP stepped down, and then declined. The maximum C_{stat} occurred at the derecruitment level (ie, around optimal PEEP) except in patients 8 and 9, in whom C_{stat} continued to rise below the optimal PEEP. This zone of maximum compliance could reflect

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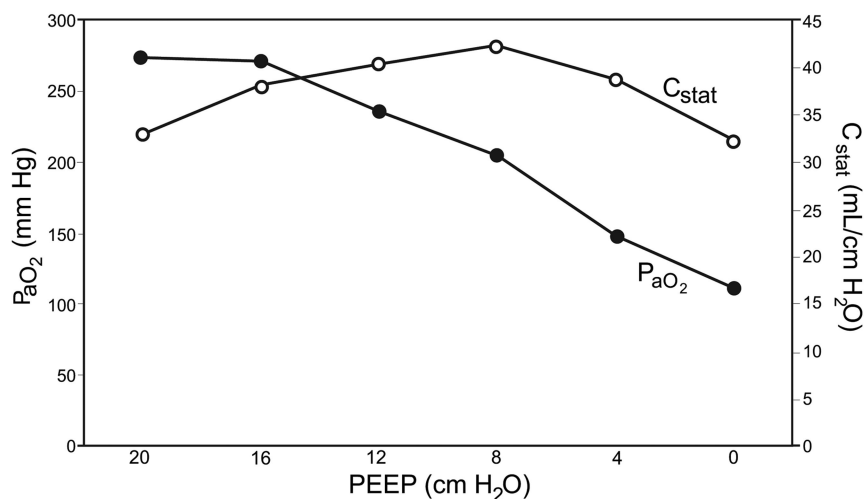


Fig. 3. Mean values of the static compliance of the respiratory system (C_{stat}) and P_{aO_2} during stepwise decrease of positive end-expiratory pressure (PEEP) in 12 patients. The standard deviations are omitted for clarity.

Table 2. Respiratory Mechanics, Hemodynamics, and Arterial Blood Gas Values With 3 PEEP Strategies

	Optimal PEEP Only (mean \pm SD)		Optimal PEEP With a Sustained Inflation (mean \pm SD)		Optimal PEEP With Sighs (mean \pm SD)	
	Baseline	60 min	Baseline	60 min	Baseline	60 min
PEEP (cm H ₂ O)	9 \pm 5	12 \pm 4	9 \pm 5	12 \pm 4	9 \pm 5	12 \pm 4
Total PEEP (cm H ₂ O)	10 \pm 4	13 \pm 4	11 \pm 4	13 \pm 4	11 \pm 4	14 \pm 4
P _{plat} (cm H ₂ O)	20 \pm 4	24 \pm 5	20 \pm 5	23 \pm 5	21 \pm 5	23 \pm 5
C _{stat} (mL/cm H ₂ O)	37 \pm 11	36 \pm 10	38 \pm 12	39 \pm 13	37 \pm 12	41 \pm 13*
Mean systemic arterial pressure (mm Hg)	78 \pm 8	78 \pm 7	77 \pm 8	75 \pm 8	78 \pm 9	81 \pm 10
P _{aO₂} (mm Hg)	111 \pm 55	140 \pm 53	114 \pm 49	160 \pm 63	110 \pm 46	182 \pm 66†
P _{aCO₂} (mm Hg)	40 \pm 8	41 \pm 8	41 \pm 8	40 \pm 8	41 \pm 8	40 \pm 10
pH	7.39 \pm 0.05	7.39 \pm 0.05	7.39 \pm 0.04	7.39 \pm 0.04	7.39 \pm 0.04	7.40 \pm 0.04

* P values (via analysis of variance) for C_{st} differences: positive end-expiratory pressure (PEEP) strategy factor effect $P = .002$; optimal PEEP with sustained inflation $P = .06$; optimal PEEP with sighs $P < .001$.

† P values (via analysis of variance) for P_{aO_2} differences: PEEP strategy factor effect $P = .001$; optimal PEEP with sustained inflation $P = .03$; optimal PEEP with sighs $P < .001$.

P_{plat} = plateau pressure

C_{stat} = static compliance of the respiratory system

the persistence of a maximum recruitment despite lower PEEP (above the point of closure), with less overdistention. Half of our patients could not receive the maximum protocol PEEP (24 cm H₂O) because of concern about their lung safety.

Superimposed sighs significantly improved oxygenation and C_{stat} , compared to one sustained inflation, at the same optimal PEEP. The improvement in oxygenation and C_{stat} with sighs may be explained by the following mechanisms, which might act concurrently.

First, the sighs recruited the lung above the optimal PEEP, which suggests a potential for lung recruitment above optimal PEEP. The ARDS lung has a low potential for recruitment: an average 9% of the lung mass in the airway pressure range 5–45 cm H₂O.²⁴ However, the po-

tential recruitment is probably greater in early ARDS,¹³ even though Gattinoni et al found no difference in recruitment between early and late ARDS.²⁴ It is likely that repetitive sighs exploited some of the lung's recruitability.

Second, optimal PEEP may maintain the recruitment elicited by sighs across the cycles, but the present data do not support that hypothesis.

Third, the repeated sighs may oppose the tendency toward lung derecruitment over time during the one-hour experimental period, by keeping the tidal ventilation along the expiratory limb of the respiratory system.²⁵

It is interesting to note that, even though the sigh V_T was limited to twice the regular V_T , only 3 patients reached the P_{plat} limit of 40 cm H₂O during sighs. Therefore, the oxygenation benefit of sighs was obtained at a low pres-

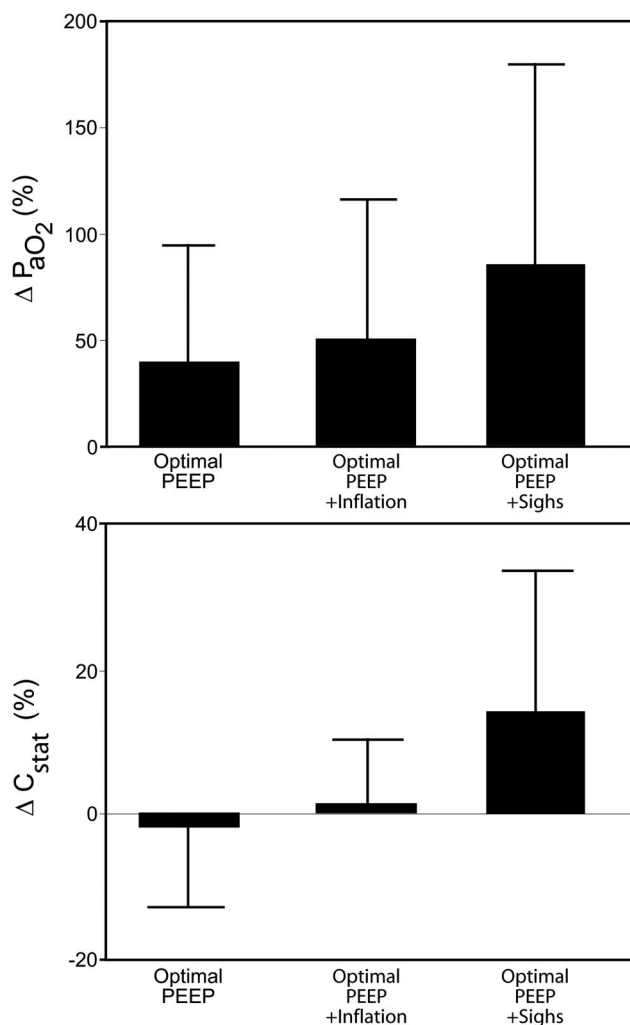


Fig. 4. Means and standard deviations of the changes in P_{aO_2} and the static compliance of the respiratory system (C_{stat}) relative to baseline (ie, before each experiment). Positive end-expiratory pressure (PEEP) strategy factor effects (via analysis of variance): $P = .001$. Optimal PEEP only versus optimal PEEP with a sustained inflation: $P = .48$. Optimal PEEP only versus optimal PEEP with superimposed sighs: $P < .001$.

sure cost. Furthermore, the risk/benefit balance for sighs in the present study was much lower than in the study by Pelosi et al, who used 3 sighs a minute, which resulted in P_{plat} of 45 cm H₂O.²⁶ A recent comprehensive study in mice suggested that deep inflations (sighs) superimposed on low- V_T ventilation prevented biotrauma by reducing lung inflammation while maintaining an open lung.²⁷ Moreover, there was a trend for an optimal frequency range of deep inflations: 2 sighs per minute was superior to 2 sighs after one hour of mechanical ventilation to reduce the lung stress.²⁷

We did not directly assess alveolar recruitment, so we cannot establish that the effects with the sighs resulted from alveolar recruitment. The fact that the oxygenation

improvement was associated with increased C_{stat} indirectly supports that hypothesis, but recruitment should have also decreased the P_{aCO_2} , which was not the case (see Table 2).

In patients with ARDS, Constantin et al recently found that both sustained inflation (at 40 cm H₂O for 40 s) and extended sighs (PEEP 10 cm H₂O above the lower inflection point of the pressure-volume curve of the respiratory system) improved oxygenation, but only the extended sighs recruited the lung.²⁸

In our study sighs were superior to sustained inflation, in that sustained inflation did not result in better oxygenation than optimal PEEP alone. Indeed, a single sustained inflation may not be comparable to repeated sighs. Alternatively, perhaps higher PEEP should be used to maintain alveolar recruitment after a single sustained inflation. In line with that hypothesis, Girgis et al found that optimal PEEP averaged 9 cm H₂O in 20 patients with ARDS, after several sustained inflations.¹⁹ However, that is the way both interventions are applied in practice.

The use of recruitment maneuvers in patients with ARDS is controversial because there is no standardization among the various recruitment maneuvers, and randomized controlled studies found that a single sustained inflation did not significantly change oxygenation, compared to high PEEP alone.¹⁸ Moreover, the response to sustained inflation was highly variable in patients with ARDS who were receiving high PEEP.²⁹ Also, some animal studies raised concerns about hemodynamic intolerance of recruitment maneuvers.³⁰⁻³² In the present study we found no serious adverse hemodynamic effects, but that assessment was based on arterial blood pressure measurement, which may underestimate the effect on cardiac performance.³³

Limitations

The present study included only 12 patients, and we did not directly assess alveolar recruitment. Moreover, oxygenation may not be an important clinical outcome for patients with ALI/ARDS, and a study of this size can't provide information on patient outcomes.

Conclusions

In patients with early ALI/ARDS and on lung-protective low- V_T ventilation, the decremental PEEP trial is an efficient and safe way to determine the patient's optimal PEEP, and superimposed sighs sustain the alveolar recruitment. However, recruitment and oxygenation may not be determinants of patient-important outcomes, such as survival.

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